

OTS: 60-41,370

JPRS: 5556

10 October 1960

THE ETIOLOGY, PATHOGENESIS, AND SURGICAL  
TREATMENT OF MALIGNANT TUMORS OF THE THYROID GLAND

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- USSR -

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JPRS: 5556

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THE ETIOLOGY, PATHOGENESIS, AND SURGICAL TREATMENT  
OF MALIGNANT TUMORS OF THE THYROID GLAND

Following is the translation of an article by  
F. A. Agafonov entitled "K Etiologii, Patogenezu  
i Khirurgicheskomu Lecheniyu Zlokachestvennykh  
Opukholey Shchitovidnoy Zhelezy" (English version  
above) in Khirurgiya (Surgery) Vol. 36, No. 5,  
1960, pp. 30-34.

From the Surgical Division (Head -- Prof. O. V.  
Nikolayev) of the clinic (Head -- Prof. Ye. A.  
Vasyukova) of the All-Union Institute of  
Experimental Endocrinology.

Malignant tumors in the thyroid gland have often owed their origin to various hormonal dysfunctions, particularly to disturbances in the interrelation of the thyreotropic function of the hypophysis and the hormone formation in the thyroid gland.

Mutually-correlative processes in the hypophysis and the thyroid gland in certain cases can actually be the cause of the arising of malignant tumors. The cells with an atypical growth which have arisen in the thyroid gland under the action of carcinogenic substances, when they are further stimulated by the thyreotropic hormone of the hypophysis, continue to develop as embryos of a malignant tumor, of which there are indications in the literature. For example, Crile in an experiment involving the disturbance of the "Thyroxin -- thyreotropic hormone" hormone balance, observed the appearance of such cells. It is generally known, that  $I^{131}$  and thiourea derivatives when they act on the cells of the thyroid gland can lead to the conversion of normal cells into atypical cells; this is particularly observed when the indicated factors are used jointly. It is assumed that when such agents act the protective barrier of the cell is first of all lowered, as a consequence of which under the action of carcinogenic substances penetrating into the cell there ensues a molecular regrouping (Rondoni, Dargent, Guinet).

Broad experimental investigations with thiourea, thyre-

otropin, and  $I^{131}$  (B. V. Aleshin, A. A. Voitkevich, and others) have shed much light and to a considerable extent have explained the cause of malignant neoplasms of the thyroid gland. It has been established by the experiments, that the maximally frequent development of adenoma (O. V. Nikolayeva and others) and their malignant degeneration ensues in the presence of iodine insufficiency. Under these conditions there is often observed a compensatory hyperplasia of the thyroid gland, which is the background for the appearance of atypical growth of the cells. In the presence of iodine insufficiency the inoculated tumor takes root considerably better (Purves), Morris, and others. It is consequently understandable that cancer of the thyroid gland is more frequently encountered not only in human beings, but also in animals in localities where goiter is endemic (I. K. Akhunbayev, Schlattauer, Sokal, and others). Parhon with coworkers, using cortisone for animal recipients, also observed a better rooting of the transplanted malignant tumors, and explained this phenomenon on the basis of the immunobiological properties of the experimental animal-recipients. The taking root of the inoculated tumor proceeds better when the animal is simultaneously irradiated with X-rays or radium rays, thereby hampering the mobilization of the protein formations in the antibodies (Wentworth and Billon). The thyreotropic hormone is often used with success in the passage of tumors. In the literature there is an indication that the prolonged use of the thyreotropic hormone without the addition of any carcinogenic substances can independently evoke the formation of a malignant tumor of the thyroid gland (Money, Rawson). Goldberg, Doniach simultaneously used 400  $\mu$ c of  $I^{131}$  in eight rats of 25 and after one and a half to two years obtained a malignant tumor of the thyroid gland (G. Morris).

The biochemistry of the cancer cell of the thyroid gland is to a considerable extent different from the biochemistry of the healthy cell. In the inoculated tumor there is observed the gradual lowering of the content of iodine, the distortion of the mechanism of binding it and a lowering of the absorption of  $I^{131}$ . The glycolysis (both anaerobic, and also aerobic) doubled (Warburg).

The biological property of epithelial cells is invariably changed when the glandular tissue is converted into a malignant tumor, according to the conviction of Wegelin. The rapidly growing adenocarcinoma and the metastases, particularly in the lymphatic nodes, ceases to concentrate  $I^{131}$  (Goldberg). It ensues from this, that the regressive degenerative process leads to the loss by the glandular cells

of their physiological specificity.

Since the synthesis of the hormone thyroxin in the cancer cells is not only distorted, but is also considerably lowered, as the tumor develops further, the changed synthesis of thyroxin also occasions a more intensive function of the basophil cells of the anterior lobe of the hypophysis which elaborate thyreotropin. The raised content in the blood of the thyreotropic hormone, apparently, stimulates the growth of normal glandular tissue, but not of the cancer cells, which have already assumed an atypical structure. Consequently if in the presence of a cancerous tumor of the thyroid gland a rise in its hormonal function is sometimes observed, this probably proceeds more due to still unchanged, but stimulated glandular tissue, than due to the tumor itself.

The process of atypical growth of the epithelial tissue itself or of certain elements of the connective tissue which has begun continues with a varying rapidity to spread irrepressibly, displacing the normal tissue.

The degree of malignancy of the tumor is determined by the intensity of growth, by the rapidity of intergrowth in the capsule of the thyroid gland and in the surrounding tissues, and also by the rapidity of the formation of metastases in various organs and tissues (Dobyns, Pemberton).

In view of the complexity of the histological structure of malignant tumors of the thyroid gland a large number of classifications have been proposed, which do not lend themselves to unification. At the basis of some classifications are placed morphological data, of others, etiological data, of a third group, functional data, of a fourth group, the degree of malignancy, of a fifth group, pathogenetical data.

If we take the classification proposed by Lahey and Hare and add to it the fourth group, then it considerably more fully embraces all the diversity of the malignant tumors of the thyroid gland.

First group: 1) papillary cystadenoma with infiltrative growth, 2) alveolar adenoma with infiltrative growth.

Second group: 1) papillary adenocarcinoma, 2) alveolar adenocarcinoma.

Third group: 1) fine cellular carcinoma, 2) giant cell carcinoma, 3) carcinoma from Hürthle cells, 4) fibrosarcoma.

Fourth group: 1) sarcoma (fine cell, coarse cell, and spindle shaped cell) 2) hemangioendothelioma, 3) flat cell cancer, 4) Langhans tumor, 5) mixed tumor, 6) metastasing adenoma, 7) Graham tumor (noncapsulated, sclerosed), 8) embryonal adenoma of Wilson.

Malignant tumors of the thyroid gland present great difficulties for early diagnosis. Certain scholars (Pemberton, Black, Perloff and Schneeberg, Horn, Chesky, and others)

consider that in many patients with malignant tumor of the thyroid gland there are hardly any clinical signs. Crile considers, that before operation one can establish a correct diagnosis only in the presence of tumors of a great degree of malignancy. For great precision of the diagnosis one might avail oneself of the property of lowering the absorption by the malignant tumor of radioactive iodine; however, it is well-known that nodes of the thyroid gland which are not malignantly degenerated also absorb  $I^{131}$  poorly.

All the generally well known signs of malignancy of the thyroid gland nevertheless are late. These include: sphericity of the node, its dense consistency, eroded boundaries of the goiter, limited mobility, tuberosity, the feeling of pressure on the trachea, hoarseness of the voice, irradiating pains, Horner's syndrome, acceleration of the erythrocyte sedimentation rate, the presence of metastases.

The maximally rational method of treatment of malignant neoplasms of the thyroid gland appears to be surgical operation with subsequent radiation therapy. However, there is no full accord concerning the methodology of the operations and the dimensions of the surgical intervention. A portion of surgeons limit themselves at the early stage of the disease to the removal of the primary focus of the malignant tumor of the thyroid gland, to an operation of the hemistru-mectomy type. However, a number of surgeons even at the beginning stage of the disease recommend the complete extirpation of the thyroid gland with the removal not only of the regional lymphatic nodes, but also those located in the mediastinum, for which section of the sternum (MacFee) and transplanting of the parathyroid glands into the muscular tissue (MacDonald) is conducted when necessary. In the presence of an infiltrative growth of a malignant tumor of the thyroid gland in the surrounding tissues and organs, the tactical approach of the surgeon is conditioned by the dimensions of the process of degeneration which has developed and by the degree of injury of the surrounding tissues and organs.

In the period of 23 years (1936-1958) in the surgical division of the clinic of the All-Union Institute of Experimental Endocrinology there were 78 patients with malignant tumor of the thyroid gland of whom 73 were operated on (five patients were sent to the Central Institute of oncology for combined treatment).

Table 1 shows the distribution of patients with respect to age and sex.

Table 1

Age	Sex		Total
	Men	Women	
Up to 10 years	-	1	1
From 11 to 20 years	1	2	3
From 21 years to 30 years	1	6	7
From 31 years to 40 years	3	19	22
From 41 years to 50 years	1	19	20
From 51 years to 61 years	7	14	21
From 61 years to 70 years	1	2	3
From 71 years and older	-	1	1
TOTAL.....	14	64	78

As is evident from Table 1, around 50 percent of the patients were from 31 to 50 years in age.

A comparatively rapid (6-10 months) development of the malignant tumor took place in 30 patients.

It is practically impossible to note the beginning conversion (term of N. N. Petrov) of the simple goiter into the malignant tumor, and consequently we shall dwell chiefly on those signs of the disease which were observed in the patients when they were admitted to the clinic: nodular enlargement of the thyroid gland (in 78 patients), unilateral nodular goiter (in 64), dense nodes, single and multiple (in 47), limitation of the mobility of the nodes (in 58), along with goiter, enlargement of the lymphatic nodes (in 37), stridorous respiration (in 29), difficulty in deglutition and the passage of food along the esophagus (in 8 patients).

During roentgenoscopy in 24 patients there was detected a constriction and displacement of the trachea and a homogeneous shadow in the mediastinum, descending at a varying depth. The malignant tumor which had grown in the mediastinum, in contrast to the simple retrosternal goiter, gave an undisplaced shadow in the presence of a cough impulse.

On the basis of the signs enumerated above, an exact diagnosis was established for 37 patients before operation, in 16 patients, the hypothesis of the presence of a malignant tumor of the thyroid gland was advanced, and in the other 25 patients, the malignant tumor was an operational find.

In 24 patients there was observed a small tachycardia (pulse 90-106 beats per minute) and a somewhat raised basal metabolism (+15 to +30%). The content of sugar in the blood

fluctuated from 80 to 120 mg%, of cholesterol - from 150 to 170 mg%. Erythrocytes were from 3,000,000 to 4,000,000 in 21 patients, greater than 4,000,000 in 52 patients; hemoglobin was 70-88%, leukocytes 4,000-10,000; erythrocyte sedimentation rate from 20-40 mm per hour. The Schilling hemogram was not different from that of healthy individuals.

We observed pathological changes in the surrounding tissues and metastases in remote organs in a majority of the patients. Thus, metastases in the regional and lymphatic nodes of the neck were observed on one side in 21 patients, on both sides of the neck -- in four patients; metastases in the bone (spine, pelvis, rib) were observed in three patients, in the lungs -- in two patients. Metastases were observed simultaneously in the lymphatic nodes of the neck, the bone, and the lungs in two patients. In 13 patients there took place growth of the tumor into the cellular tissue of the mediastinum, in three -- of the vascular bundle of the neck, in five -- of the trachea, and in one patient -- of the esophagus. Thus, in 24 patients the tumor was located only in the thyroid gland, in 19 patients its growth into the surrounding tissues and organs was observed, in 35 patients metastases were detected both into the regional lymphatic nodes, and also into remote organs. The neglected state of the disease in a significant majority of the patients, unfortunately, excludes the possibility of drawing conclusions concerning the initial signs of the disease.

Our many years of experience pertaining to the observation of the dynamics of the disease permits us to recommend surgical treatment to all patients with nodular goiter, without waiting for any other signs of malignancy -- that is also the very best method of cancer prophylaxis.

After the clinical examination had been conducted, 73 patients were operated on under local anesthesia with an 0.5% solution of novocaine, and around 70 percent of the patients were operated on in response to urgent indications.

The following operations were conducted: extirpation of the tumor and enlarged lymphatic nodes in 38 patients, extirpation of the tumor from the surrounding tissues and in part the organs into which it had grown (veins, esophagus) -- in 16, enucleation of one node of the thyroid gland -- in 10, enucleation of several nodes of the thyroid gland -- in four, partial resection of the tumor -- in five, repeated operations in the presence of relapses -- in seven patients.

One patient [female] who was repeatedly operated on for the course of 10 years underwent four operations: one extirpation of a malignant tumor of the thyroid gland and three operations for the removal of relapses of a tumor in the

lymphatic nodes of the neck. Three patients underwent three operations each (one of them was twice operated on on account of a relapse at the site of the removed metastases of a tumor in the lymphatic nodes of the neck). Three patients were operated on twice: the first time a malignant tumor was removed from their thyroid gland and the second time, having relapsed, a tumor was removed which had developed at the site of the removed tumor in the tissue of the thyroid gland. All the enumerated patients are continuing to work.

The malignant tumors of the thyroid gland, which had been diagnosed before operation, were extirpated within the limits of the healthy tissue with the removal of all accessible enlarged lymphatic nodes of the neck and the mediastinum, without sectioning the sternum and the clavicles. The histological investigation (before 1948 -- B. N. Mogil'nitskii, from 1948 on -- Ye. I. Tarakanov) revealed the following: metastasizing adenoma -- in 15 patients, cancer (without exact differentiation) -- in 19, adenocarcinoma -- in 10, papillary cancer -- in seven, polymorphocellular cancer -- in one, follicular cancer -- in nine, flat cellular cancer -- in one, carcino-sarcoma -- in one, sarcoma (round cell and spindle-like cell) -- in seven patients.

For the overwhelming majority of the patients, X-ray therapy in the Institute of Endocrinology, in the Central Institute of Roentgenology, or at the site of the dwelling was conducted after the operation.

The results of the treatment of the patients are presented in Table 2.

### Conclusions

1. In the overwhelming majority of cases, malignant tumors of the thyroid gland develop from preceding nodular goiter.
2. In the presence of the smallest suspicion of a malignant tumor of the thyroid gland of the patient it is necessary to operate.
3. The following symptoms serve as an indication for urgent operation: sudden intensification of the growth of the goiter, acquisition by the goiter of roundness and tubercosity, diminution of displaceability and mobility, increase in the density, the growth of compression of the trachea, the appearance of irradiating pains, hoarseness of the voice, difficulties of breathing and deglutition, and painfulness in the presence of palpation at the sites of great density.



Table 2

Number of patients operated on	Number who re-covered	Period of observations (in years)				Number of patients continuing treatment (radiotherapy, repeated operations)	Period of observations (in years)				Number who died	Period which has passed after the operation (in years)			
		1	3	5	10		3	5	10	1		2	3	5	
73	46	12	19	10	5	10	6	2	2	17	11	3	2	1	

4. After the radical removal of a malignant tumor of the thyroid gland, the X-ray therapy which is being conducted acts favorably in the sense of preventing tumor relapses.

5. If growth of the malignant tumor into the surrounding tissues and organs is detected during the operation, the entire tumor should be removed within the limits of the healthy tissues. Such a tactical approach permits one not only to prolong the life of the patient for a long time, but also to preserve the patient's work capacity.

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